

PATENT COOPERATION TREATY

REC'D 07 SEP 2004

From the
INTERNATIONAL SEARCHING AUTHORITY

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To:

see form PCT/ISA/220

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**
(PCT Rule 43bis.1)

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No.
PCT/US2004/001234

International filing date (day/month/year)
15.01.2004

Priority date (day/month/year)
16.01.2003

International Patent Classification (IPC) or both national classification and IPC
C07D211/06, A61K31/4468, A61P25/14, A61P25/16, A61P25/18, A61P25/28, A61P25/24, A61P25/06

Applicant
ACADIA PHARMACEUTICALS INC.

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☒ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1bis(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:



European Patent Office
D-80298 Munich
Tel. +49 89 2399 - 0 Tx: 523656 epmu d
Fax: +49 89 2399 - 4465

Authorized Officer

Albayrak, T

Telephone No. +49 89 2399-7549



**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/US2004/001234

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.
 - ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).
2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:
 - a. type of material:
 - ☐ a sequence listing
 - ☐ table(s) related to the sequence listing
 - b. format of material:
 - ☐ in written format
 - ☐ in computer readable form
 - c. time of filing/furnishing:
 - ☐ contained in the international application as filed.
 - ☐ filed together with the international application in computer readable form.
 - ☐ furnished subsequently to this Authority for the purposes of search.
3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
4. Additional comments:

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/US2004/001234

Box No. II Priority

1. ☒ The following document has not been furnished:

☒ copy of the earlier application whose priority has been claimed (Rule 43*bis*.1 and 66.7(a)).

☐ translation of the earlier application whose priority has been claimed (Rule 43*bis*.1 and 66.7(b)).

Consequently it has not been possible to consider the validity of the priority claim. This opinion has nevertheless been established on the assumption that the relevant date is the claimed priority date.

2. ☐ This opinion has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rules 43*bis*.1 and 64.1). Thus for the purposes of this opinion, the international filing date indicated above is considered to be the relevant date.

3. Additional observations, if necessary:

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/US2004/001234

Box No. III Non-establishment of opinion with regard to novelty, inventive step and Industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 9-85

because:

☒ the said international application, or the said claims Nos. 9-85 (industrial applicability) relate to the following subject matter which does not require an international preliminary examination (*specify*):

see separate sheet

☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the whole application or for said claims Nos.

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form

☐ has not been furnished

☐ does not comply with the standard

the computer readable form

☐ has not been furnished

☐ does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-bis of the Administrative Instructions.

☐ See separate sheet for further details

**WRITTEN OPINION OF THE
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International application No.
PCT/US2004/001234

**Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or
Industrial applicability; citations and explanations supporting such statement**

1. Statement

Novelty (N)	Yes: Claims	1-8,14-16,21-24,29-31,36-38,45-86
	No: Claims	9-13,17-20,25-28,32-35,39-44
Inventive step (IS)	Yes: Claims	1-8,14-16,21-24,29,30,36-38,45,47-86
	No: Claims	9-13,17-20,25-28,31-35,39-44,46
Industrial applicability (IA)	Yes: Claims	1-8,48,86
	No: Claims	-

2. Citations and explanations

see separate sheet

Re Item I

The basis of this written opinion is the application as originally filed.

Re Item III

The subject-matter of claims 9-47, 49-85 is related to subject-matter considered to be covered by the provisions of Rule 67.1 (iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4) (a) (I) PCT).

Claim 16 does not meet the criteria of Art. 6 PCT. The claim is dependent on claim 9 and "a reagent" is defined. However, claim 9 does not claim such a reagent. Claim 16 is therefore not clear.

Re Item V

Reference is made to the following documents; unless otherwise indicated, reference is made to the relevant passages emphasized in the Search Report.

- D1: US-A-5 877 173 (FARBER NURI B ET AL) 2 March 1999 (1999-03-02)
- D2: US-A-3 983 234 (SAYERS ANTHONY CAMPBELL) 28 September 1976 (1976-09-28)
- D3: FRIEDMAN J H: "Clozapine treatment of psychosis in patients with tardive dyskinesia: report of three cases" MOVEMENT DISORDERS OFFICIAL JOURNAL OF THE MOVEMENT DISORDER SOCIETY, vol. 9, no. 3, 1 May 1994 (1994-05-01), pages 321-324, XP009032726
- D4: YOSHIDA K ET AL: "Marked improvement of tardive dyskinesia after reopacing haloperidol with risperidone in a schizophrenic patient" CLINICAL NEUROPHARMACOLOGY, vol. 21, no. 1, 1998, pages 68-69, XP009032725
- D5: DELECLUSE F ET AL: "A case of tardive tremor successfully treated with clozapine" MOVEMENT DISORDERS OFFICIAL JOURNAL OF THE MOVEMENT DISORDER SOCIETY, vol. 13, no. 5, September 1998 (1998-09), pages 846-847, XP009032724
- D6: FACTOR S A ET AL: "Clozapine prevents recurrence of psychosis in Parkinson's disease" MOVEMENT DISORDERS OFFICIAL JOURNAL OF THE MOVEMENT DISORDER SOCIETY, vol. 7, no. 2, 1992, pages 125-131, XP009032679
- D7: FACTOR ET AL: "Clozapine for the treatment of drug-induced psychosis in

Parkinson's disease: results of the 12 week open label extension in the PSYCLOPS trial" MOVEMENT DISORDERS OFFICIAL JOURNAL OF THE MOVEMENT DISORDER SOCIETY, vol. 16, no. 1, January 2001 (2001-01), pages 135-139, XP009032680

D8: US 2002/165225 A1 (KANKAN RAJENDRA N ET AL) 7 November 2002 (2002-11-07)

D9: US-B-6 358 6981 (BRANN MARK R ET AL) 19 March 2002 (2002-03-19)

D10: HERRICK-DAVIS ET AL: "Inverse Agonist Activity of Atypical Antipsychotic Drugs at Human 5-Hydroxytryptamine_{2C} Receptors" THE JOURNAL OF PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS, vol. 295, no. 1, October 2000 (2000-10), pages 226-295, XP001182089

1. Novelty

The subject-matter of claims 9-13,17-20,25-28,31-35,39-44 is not novel.

- D1 discloses the treatment of Alzheimer with olanzapine, clozapine and fluperlapine. These drugs are known as being 5-HT_{2C} and 5-HT_{2A} inverse agonists (see also D9 and D10).
- D2 discloses the treatment of dyskinesia induced by dopaminergics via the administration of clozapine.

Claims 9-13 and 17-20 are therefore not novel.

- D3 discloses the treatment of dystonia with clozapine.
- D4 discloses the treatment of dystonia with risperidone. (The drug is a 5-HT_{2C} and 5-HT_{2A} inverse agonist).
- D5 discloses the treatment of tremor with clozapine.

Claims 25-28 are therefore not novel.

- D6 discloses the treatment of psychosis, associated with dopaminergic therapy via the administration of clozapine.
- D7 discloses the treatment of drug-induced psychosis in Parkinson-patients via the administration of clozapine.

Claims 32-35 and 39 are therefore not novel (Claim 39 depends on claim 32).

- D8 discloses olanzapine for the treatment of schizophrenia and psychosis associated with Alzheimer.
- D9 discloses 5-HT_{2A} and 5-HT_{2C} inverse agonists (see columns 16 and 17, tables 2 and 3) for the treatment of psychosis and schizophrenia.

Claims 32-35, 39 and 40-44 are therefore not novel.

2. Inventive step

- Claim 46 is not inventive.

A combination of an inverse agonist selective for a serotonin receptor and a further therapeutic agent for the treatment of a neuropsychiatric disease is claimed. Both, the inverse agonist and the claimed compounds are known and even for the claimed treatment.

An inventive step could only be regarded if a surprising/unexpected effect could be shown (e.g. a synergistic activity). However, this appears not to be the case.

3. The documents WO03/070246 und WO03/062206 could become relevant in some member-states.